Claims 1-5, 7-12 and 14-19 have been rejected under 35 U.S.C. 103(a) as obvious in light of the Inventi patent, the Dickens reference, and the Stassi reference in view of Hwang, Kaur, or Caruso.

It is submitted that the Inventi patent discloses a DNA molecule that encodes daunorubicin-14-hydroxylase. It is observed that the Hwang reference discloses that doxorubicin resistance genes drrA and drrB endow a host cell with a high level of resistance to doxorubicin. It is noted, however, that the alkavinone-11-hydroxylase gene (dnrf) disclosed in Hwang does not confer doxorubicin resistance to the host cell, similar to the daunorubucin 14-hydroxylase gene (dxrA) of the Inventi reference. Therefore, it is submitted that there is no motivation to combine these references as neither dnrf or dxrA confer doxorubicin resistance, a required element of the claimed invention, and that the rejection is improper for this reason.

Additionally, it is noted that the citation of the Hwang reference is improper because Hwang is directed towards a hydroxylase (which is different from that of the claimed invention) that is also present in another step of doxorubicin biosynthesis, as shown in Figure 1 on page 1617 of Hwang. Contrary the assertions of the Examiner, the Hwang reference also does not teach an increase in an intermediate anthracycline. Hwang only teaches that DNA fragments carrying drrA and drrB also contain the alkavinone 11-hydroxylase gene which is then isolated and used alone to transform *S. galilaeus* for producing new 11-hydroxyaclacinomycin A (see page 1618 of Hwang). Therefore, it is submitted that the rejection is improper because the Hwang reference is

directed towards unrelated subject matter and because there is no motivation contained therein to combine it with the remaining cited references to produce the claimed invention.

Inventi teaches and claims an isolated DNA molecule encoding a daunorubicin 14-hydroxylase, but as discussed above, this gene is doxA (formerly dxrA) and does not confer doxorubicin resistance to the host cell. This gene encodes the amino acid sequence of 14-hydroxylase which is the enzyme involved in the bioconversion of daunorubicin into doxorubicin. As seen in the present specification, the doxA gene is used as a control in Example 4 of the present application. It is contained in the vector named pIS70 (see FIG 1a). As Table 2 on page 14 of the present application shows, the transformed strains of the present invention have a bioconversion efficiency that is about 50-60 times higher than that of the prior art (including the control), which is clearly superior and unexpected. Therefore, it is submitted that the rejection is improper because the cited art does not disclose any suggestion that the claimed combination of elements would result in such a dramatic difference in results.

Regarding the Stassi reference, this reference teaches that the ermE* promoter can be used in the production of 6,12-dideoxyerythromycin A. Additionally, Stassi indicates that *Saccharopolyspora erythraea* is preferred and uses *Saccharopolyspora erythraea* in the disclosed examples. Regardless, it is submitted that there is absolutely no suggestion or motivation in any of the references to combine the well known ermE* promoter with drrA, drrB, drrC, or doxA. Therefore, it is submitted that the obviousness

rejection should be withdrawn for this reason because the cited combination of references fail to teach all of the claimed elements.

Finally, as stated above, the Inventi reference describes and claims an isolated DNA molecule that encodes a daunorubicin 14-hydroxylase, which is used in the bioconversion of daunorubicin into doxorubicin. The method used therein for producing doxorubicin uses vectors containing isolated DNA of *Streptomyces lividans* ZX1 and *Streptomyces peucetius dnr*N. The quantity of daunomycin added to both strains in the Inventi reference for the bioconversion was 20 mcg/ml, with conversion yields of 22 and 100%, respectively. The vector used therein already carries a resistance gene and the cited prior art does not teach the replacement of the gene with drrA or drrB, as in the present invention. Therefore, the rejection should be withdrawn for this reason, as well, because the cited combination fails to teach all of the claimed elements.

It is also noted that DNA combination of claims 1-7 comprises a DNA region that is not described or suggested at all in the prior art. This region comprises the fragments named dnrV and ΔdnrU which are contained in the 2.9kb fragment together with the doxA (see SEQ ID NO.1 and the description on page 3 of the specification).

As for the remaining cited references, it is noted that the Dickens reference contains the same limitations as Inventi and also that the Kaur and Caruso references suffer from the same deficiencies as Hwang. Additionally, Caruso is no different from the '564 patent and deals with resistant genes. Therefore, Caruso is not relevant to the present invention for the same reasons stated above regarding the '564 patent. Also,

neither Caruso or Kaur teach or suggest the combination of resistant genes with doxA, dnrV and ΔdnrU in order to improve the bioconversion activity of the untransformed cells.

Therefore, for the reasons set forth above, it is submitted that these remaining references do not correct any of the deficiencies of the previously discussed references and that the rejection is improper because the combination of the references fail to provide motivation to produce the claimed invention. It is also submitted that the rejection is improper because the combination of the references fails to teach every limitation of the claimed invention. Therefore, it is submitted that the Kaur, Caruso and Dickens references could only have been cited with the use of impermissible hindsight and it is requested that the rejection be withdrawn for this and the previously stated reasons.

Claims 6 and 13 have been rejected as obvious under 35 U.S.C. 103(a) in light of the Inventi, Dickens, Stassi, Caruso, and Lomovskaya references. Applicant relies upon its previous discussion of the first four cited references in responding to the present rejection.

Lomovskaya is cited for its disclosure of the drrC gene. Because the host cells of Inventi can be DNR or DXR sensitive and because the Inventi vectors do not contain drrA, drrB or drrC, it is submitted that the Inventi host cells possess another mechanism that confers DNR sensitivity or removes DXR sensitivity from the host cells. In view of this, it is submitted that one of ordinary skill in the art would not have been motivated to

add drrA, drrB, and/or drrC to the Inventi host cells, because the Inventi host cells already possess DNR or DXR resistance. None of the cited references cure this deficiency. Further, Stassi does not suggest combining his promoter with drrA, drrB or drrC and thus cannot cure the deficiencies. Therefore, it is submitted that for this reason and the reasons already presented, that the cited combination of references cannot render the claimed invention obvious because the cited combination fails to teach all of the limitations of the present claims.

In the event this response is not considered to be timely filed, Applicants hereby petition for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300 along with any other fees which may be required with respect to this application.

Respectfully submitted,
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Attachments: Petition for Extension of Time (Three Months)